SFVAMC/DoD Collaboration

Research Program in Neuroscience

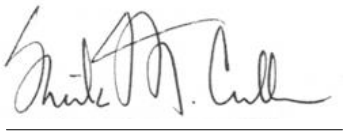
Greetings and Welcome,

On behalf of the San Francisco VA Medical Center and the Northern California Institute for Research and Education, we are delighted to welcome you to our Neuroscience Center of Excellence.

We are extremely proud and excited to present our collaborative research program with the United States Department of Defense, which is made possible by a unique partnership with the United States Army Medical Research and Materiel Command. We welcome this opportunity to present the work of our principal investigators in support of our military personnel, veterans, and the general public.

We hope you find this summary most informative and enjoyable, and look forward with enthusiasm to a healthier tomorrow.

Sincerely,



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Research Program in Neuroscience

Recognized as a "Neuroscience Center of Excellence" by the Department of Defense, the SFVAMC and its affiliated non-profit research corporation, the Northern California Institute for Research and Education (NCIRE), have been successful in establishing a collaborative agreement that brings joint VA and DoD resources together to conduct medical research in prominent health areas affecting active military, veterans and the general public.

In recognition of DoD funds administered through NCIRE, the institute has worked in collaboration with the US Army Medical Research and Materiel Command in establishing the Neuroscience Center of Excellence dedicated to conducting research collectively focused on issues in the neurosciences and neuroimaging, including mechanisms of brain and spinal cord injury, development of novel neuroprotective agents, post-traumatic stress disorder (PTSD), Gulf War Illness, other neurological combat related injuries and predictors of injuries in warfighters. Research projects represent a spectrum of investigation, ranging from basic laboratory science to clinical research.

Through NCIRE, three consecutive years of DoD funding totaling approximately $10 million have been secured to pursue research in the following areas:

FY 2003

PI: Michael Weiner, MD

Project: Initial project for research into Gulf War Illness. Work on neurobiology of soldier deployment hazards, a continuation and expansion of the current research made possible by the magnet imaging and associated technologies. Further develop diagnostic, prognostic and treatment strategies for preventable conditions in future deployments and for the post deployment health monitoring of our armed services.

Funding: $4 million

Scope: Acquisition and conduct of research using a 4 Tesla MRI/MRS system.

FY 2004

PI: Michael Weiner, MD (Primary PI)

Funding: $3.25 million

PI	Title
Raymond A. Swanson, MD	Promoting neurogenesis by suppressing microglial activation
Steven W. Cheung, MD	Repetitive Transcranial Magnetic Auditory Cortex Stimulation for Tinnitus Suppression
Jialing Liu, PhD	The role of corpus callosum in mediating functional recovery after traumatic brain injury
Charles R. Marmar, MD	Cognitive Behavior Therapy and D-Cycloserine Treatment of PTSD in OEF and OIF Veterans.
Dieter J. Meyerhoff, Dr.rer.nat.	Brain GABA and glutamate in acute PTSD
Rajabrata Sarkar, MD, PhD	Matrix Metalloproteinase Therapy for Traumatic Limb Ischemia
S. Scott Panter, PhD	Direct Delivery of Neurotoxins to the Brain by an Intranasal Route
Stephen Massa, MD, PhD	Novel Neuroprotective and Regenerative Agents for Head and Spinal Cord Injury
C. Seth Landefeld, MD (Co-Investigators: Kenneth E. Covinsky, MD, Mary Margaret Chren, MD, Michael Shlipak, MD, and Kristine Yaffe, MD	Predictors of Injury in Warfighters: A VA-DOD Collaboration

FY 2005

PI: Michael Weiner, MD

H. Jeffrey Lawrence, MD, Co-PI

Funding: $3.52 million

PI	Title
Lilly Bourguignon, PhD	Novel Astrocyte Signaling Therapy to Promote Neuronal Regrowth and Suppress Glial Scarring During Traumatic Brain Injury
Valerie Cardenas-Nicolson, PhD	Patterns of MRI Brain Atrophy Rate in PTSD
Linda L. Chao, PhD	Functional MRI of Emotional Memory in Veterans With And Without Posttraumatic Stress Disorder
Rajvir Dahiya, PhD	Improve function of spinal cord injury-induced neurogenic bladder
Peter Elias, MD	Novel Approach to Overcoming Psychological Stress-Induced Delays in Wound Healing by Inhibiting Stress Hormone (Glucocorticoid) Activities
Grant Gauger, MD	The Post-Traumatic Syndrome of Blunt Head Injury: Noninvasive Neurochemical and Structural Assessment
Norbert Schuff, PhD	Parkinsonism as Model to Detect Neurodegeneration by High Field MRI
Karen Seal, MPH, MD	The Neuropsychiatric Consequences of War: Investigating the Relationship between PTSD and Alcohol Abuse among Veterans Returning from Iraq and Afghanistan
William Seaman, MD	Role of TREM-2 in the Microglial Response to Injured Neurons

November 9 will be NCIRE's DoD Investigator day, showcasing PI's and their projects with USAMRMC representatives.

Investigating Changes in the Brain Associated with Gulf War Illness

Michael Weiner, MD

Director of the Center for Imaging of Neurodegenerative Disease, SFVAMC

Professor of Radiology, Medicine, Psychiatry, and Neurology, UCSF

Some veterans of the Gulf War subsequently developed a wide variety of physical and neuropsychological symptoms, termed Gulf War Illness. Several investigators have attributed these symptoms to stress; however, other data indicate physical changes in the brains of some subjects, primarily reductions of the neuronal marker N-acetyl aspartate, a marker of neuron integrity and density, in the basal ganglia and pons. One limitation of previous studies was that they did not control for posttraumatic stress disorder, depression, or alcoholism, which also cause structural and metabolic changes in the brain. This goal of this research project is to use magnetic resonance imaging technology to test the hypothesis that subjects with Gulf War Illness have metabolic and/or morphological changes in their brains that are not accounted for by other factors. A secondary goal is to determine if these brain changes correlate with central nervous system signs and symptoms of Gulf War Illness. If these hypotheses prove correct, this study has the potential to yield new diagnostic and treatment tools and strategies not only for veterans of the Gulf War, but for military personnel who have served and are serving in the current Iraq war zone.

Changes in Brain Anatomy During the Course of PTSD

Valerie Cardenas-Nicolson, PhD

Staff Researcher, Mental Health Service, SFVAMC

Assistant Adjunct Professor of Radiology, UCSF

Patients with posttraumatic stress disorder exhibit a wide range of neuropsychological deficits. Atrophy in brain regions such as the hippocampus has also been reported. Although there have been many magnetic resonance image studies of PTSD, most have involved cross-sectional analyses of just a few pre-selected regions of the brain. A three-dimensional imaging technique called voxel-wise structural image analysis provides a way of looking for anatomical variation in the brain without prior hypotheses about the location and extent of the variation. This research project will use this technique to investigate the spatial patterns of tissue atrophy rate in participants with PTSD compared to participants without PTSD. Additionally, the study will correlate participants' performance on neuropsychological tests with visual evidence of neurodegeneration. **The results of this project will lead to a better understanding of the course of PTSD over time and its relation to underlying brain anatomy.**

New Treatment for Posttraumatic Stress Disorder

Charles R. Marmar, MD

Staff Physician, Associate Chief of Staff of Mental Health, SFVAMC

Professor and Vice Chair of Psychiatry, UCSF

At least 400,000 Americans are expected to serve in Iraq and Afghanistan; of those, approximately 17 percent are expected to return with posttraumatic stress disorder (PTSD). This research project will compare the effectiveness of cognitive behavior therapy (CBT)—the current standard treatment for PTSD—with CBT in combination with D-Cycloserine (DCS), a widely-available, safe, and low-cost drug that holds the promise of making treatment both quicker and longer-lasting. DCS belongs to a class of drugs known as NMDA receptor partial agonists, which affect the underlying brain mechanism that controls how quickly fears can be unlearned. **The goal of the study is to test the hypothesis that DCS in combination with CBT will more quickly and effectively prevent veterans of Iraq and Afghanistan from developing the chronic, long-term, and highly disabling form of PTSD that has damaged the lives and health of an estimated 850,000 veterans of the war in Vietnam.** If successful, the study will serve as a foundation for larger studies at Veterans and Department of Defense medical sites around the United States.

The Role of Neurotransmitters in PTSD

Dieter Meyerhoff, Dr.rer.nat.

Senior Researcher, Radiology Service, SFVAMC

Professor of Radiology, UCSF

The neurotransmitters GABA and glutamine are critical for registering emotion and for encoding memories of emotion and fear. Imbalances and long-term dysfunction in these neurotransmitters and related cell death are believed to explain the clinical symptomology of posttraumatic stress disorder (PTSD), which is expected to affect up to 17 percent of veterans returning from combat in Iraq and Afghanistan. This research study will use the 4Tesla magnetic resonance scanner at SFVAMC to measure GABA, glutamine, and the neuronal marker N-acetylaspartate in returning Iraqi war veterans with and without PTSD. **The aims of this study are to illuminate the roles of GABA and glutamine in PTSD and to identify potential objective markers of PTSD-related brain injury and potential treatment responses.** Some study participants with PTSD will also participate in the CBT/cycloserine clinical treatment trial at SFVAMC (PI: Charles Marmar, MD).

A Possible Biomarker for PTSD

Linda Chao, PhD

Assistant Research Scientist, Radiology Service, SFVAMC

Associate Adjunct Professor of Radiology and Psychiatry, UCSF

This research project will use the technique of functional magnetic resonance imaging to examine the effect of posttraumatic stress disorder on the way signals are processed in a high-level visual processing area of the brain. Specifically, the pattern of blood-oxygen level dependent (BOLD) response in the lateral occipital complex will be compared in combat veterans with PTSD and combat veterans without PTSD as they view pictures with and without combat-related content in different presentation conditions. The hypothesis is that veterans with PTSD will show smaller decreases over time in BOLD response to combat-related pictures than to non-combat pictures. **If this hypothesis proves to be a truly robust and reproducible finding, it may be a useful biomarker for validating self-reported measures of PTSD and of PTSD treatment efficacy.**

Improved Understanding of Post-Concussion Syndrome

Grant Gauger, MD

Staff Physician, Surgical Service, SFVAMC

Clinical Professor of Neurological Surgery, UCSF

Blunt trauma of the human brain, which occurs in a wide variety of military operations, presents serious problems in assessment, treatment, and outcome prediction. Mild traumatic brain injury—concussion—is frequently followed by a clinical syndrome that is associated with serious disability, despite the absence of significant abnormalities on conventional radiologic imaging. Previous studies of concussion subjects using 1.5 Tesla magnetic resonance imaging have revealed evidence of widespread metabolic changes. In order to clarify the extent and significance of such changes, this research project will study concussion subjects using a higher-resolution 4 Tesla MRI system, with repeat testing at six months after injury. The study will also employ diffusion tensor imaging (DTI) to study white matter fiber systems in the brain. MRI and DTI data will be correlated with neurocognitive and psychological testing. **This research is anticipated to lead to improved understanding of post-concussion syndrome, with early application to important decisions in the assessment and treatment of injured military personnel.**

Evaluating the Neuropsychiatric Consequences of War

Karen Seal, MD, MPH

Staff Physician, Medical Service, SFVAMC

Adjunct Assistant Professor of Medicine, UCSF

A substantial proportion of Afghan and Iraq veterans suffer from one or more neuropsychiatric illnesses, especially posttraumatic stress disorder, depression, and alcohol use disorders. Due to various barriers to care, especially stigma, only a minority of affected vets have received treatment, potentially foreshadowing a large-scale public health problem. Recently, the Veterans Health Administration instituted the "Afghan and Iraq Post-Deployment Screen" to screen for these disorders among returning vets. However, the prevalence and predictors of positive screens for these three target disorders have not been determined; rates of co-morbidity are unknown; and the associated levels of physical, psychosocial, and occupational impairment have not been studied. In addition, it is not known whether veterans who screen positive for neuropsychiatric illnesses receive VA mental health treatment, and if not, why not. This research study proposes to analyze the VA post-deployment screening data to determine the scope of neuropsychiatric illness and conduct a more in-depth telephone survey of enrolled Afghan and Iraq vets to evaluate specific determinants of neuropsychiatric illness and barriers to early treatment. **The long-term objective of this research is to prevent an epidemic of chronic neuropsychiatric illness among veterans of Afghanistan and Iraq by identifying high-risk individuals and developing cost-effective treatment interventions.**

Promoting Neuron Growth by Suppressing Brain Inflammation After Injury

Raymond Swanson, MD

Staff Physician, Chief of Neurology and Rehabilitation Service, SFVAMC

Professor and Vice Chair of Neurology, UCSF

There is widespread enthusiasm for neurogenesis—the innate ability of the brain to generate new neurons—as an approach to facilitating rehabilitation after brain injury. However, neurogenesis is suppressed by the brain inflammatory response, which is mediated primarily by activated microglia, the immune cells of the central nervous system. Brain inflammatory response is necessary for fighting infection but counterproductive in conditions such as stroke, brain trauma, and Alzheimer's disease. This research project aims to apply a novel method of suppressing microglial activation, and therefore inflammatory response, in a rodent model of stroke through the suppression of PARP, a DNA repair enzyme. The goal is to test the effect of this approach on neurogenesis and functional recovery. The study would also extend this approach to rodent models of brain trauma. **Success in these areas would have far-reaching implications for the field of neurogenesis and neuro-rehabilitation, which would be potentially of great importance for the treatment of battlefield brain injury.**

Potential New Treatments for Brain and Spinal Cord Injury

Stephen Massa, MD, PhD

Staff Physician, Neurology Service, SFVAMC

Clinical Assistant Professor of Neurology, UCSF

Neurotrophins—molecules such as nerve growth factor and brain-derived neurotrophic factor that promote the growth and survival of nerve cells—have shown great promise in the laboratory as treatments for a variety of nervous system disorders, including traumatic brain and spinal cord injury, for which combat personnel are at high risk. However, a number of unfavorable pharmacologic properties have stalled their clinical application. This research project will investigate the potential clinical effectiveness of molecules that modulate specific neurotrophin receptors in nerve cells. **These molecules have potent neurotrophic activity on their own and could potentially be administered in place of neurotrophins to treat traumatic brain and spinal cord injury.** This research project will further validate the therapeutic potential of these novel compounds and possibly point to in vivo pharmacologic challenges requiring further investigation—both important checkpoints in their progression toward clinical application.

Investigating Mechanisms of Inflammatory Response to Brain Injury

William Seaman, MD

Staff Physician, Chief of Immunology Section, SFVAMC

Professor of Medicine and Microbiology/Immunology, UCSF

Microglia are brain cells that monitor the brain environment, support neuronal function, remove damaged neurons, and initiate inflammation, which is an essential response to infection but can prevent complete recovery from other kinds of brain trauma. TREM-2, a cell-surface receptor that plays a crucial role in regulating microglial response to brain injury, has been shown to regulate and prevent inflammatory response. This research project will investigate the mechanism by which TREM-2 regulates this response. **Through a variety of research approaches, this study will define new pathways for regulating the microglial response to brain injury. The results of this research will potentially have positive consequences for the treatment of brain injury among military personnel.**

Brain Cell Regeneration and Recovery from Traumatic Brain Injury

Jialing Liu, PhD

Research Fellow, Surgical Service, SFVAMC

Associate Professor of Neurological Surgery, UCSF

Traumatic brain injury is a serious and disabling injury that frequently occurs in soldiers during combat. The normal functional balance of the two hemispheres of the brain can be disrupted through injury to one hemisphere, resulting in limb disability on one side of the body. **There is emerging evidence from stroke patients that recovery from this type of injury is enhanced through constraint-induced therapy (CIT), the forced use of the affected limb through immobilization of the healthy limb, which increases cortical excitability in the uninjured hemisphere of the brain.** There is also evidence that CIT enhances brain cell regeneration. The aims of this research project are to (1) test the hypothesis that CIT enhances neuronal regeneration and functional recovery after traumatic brain injury and (2) test the hypothesis that increased cortical excitability in the uninjured hemisphere is mediated through the corpus callosum, the structure that connects the right and left cerebral hemispheres.

Promoting Neuronal Regrowth and Suppressing Scarring After Traumatic Brain Injury

Lilly Y.W. Bourguignon, PhD

Career Scientist, Medical Service, SFVAMC

Professor of Medicine, UCSF

Serious cererbrovascular insults such as traumatic brain injury cause a breakdown of the blood-brain barrier and thus allow blood-derived substances direct access to neurons and the glial (non-neuronal) brain cells called astrocytes. This access can cause astrogliosis or glial scarring, which in turn can interfere with neuronal growth and regeneration of nerve fiber after central nervous system injury. A key to this scarring process is the interaction between hyaluronan, a compound found in the extracellular matrix of tissues throughout the body, and CD44, a surface receptor molecule that plays an important role in a variety of cellular activities and functions. This research project will focus on that interaction and how it might be modified in order to promote regrowth of neurons and suppress astrogliosis. **A better understanding of the basic cellular and molecular mechanisms that initiate and control these healing and scarring processes may lead to important advances in the treatment of central nervous system damage such as traumatic brain injuries suffered in combat by military and civilian personnel.**

A Potential New Treatment for Spinal Cord Injury-Related Bladder Dysfunction

Rajvir Dahiya, PhD

Research Scientist, Medical Research Service, SFVAMC

Professor of Urology, UCSF

Currently, thousands of our veterans suffer from neurogenic bladder—loss of normal bladder function—as a result of combat-related spinal cord injury. Treatment is limited. This research project will investigate the hypothesis that the function of spinal cord injury-mediated neurogenic bladder can be improved by grafting with acellular bladder matrix, an artificial matrix for cell growth. Using animal models, the study will test the effectiveness of this grafting technique. The project will also investigate the effectiveness of the growth factors TGFb1, VEGF, and EGF in accelerating the ingrowth of smooth muscle, bladder lining, blood vessels, and nerves in the regeneration of a new, functional bladder. **If successful, this research holds the potential for development of new treatments for spinal cord injury-mediated neurogenic bladder.**

Treating Tinnitus in Military Personnel

Steven W. Cheung

Staff Physician, Surgical Service, SFVAMC

Associate Professor of Otolaryngology, UCSF

Tinnitus, or ringing in the ear, affects 10 to 15 percent of the population as a whole. Twenty percent of those patients experience insomnia, hearing loss, mood disorders, and cognitive disturbances. While there are treatments, there is currently no effective medical or surgical therapy for unremmiting tinnitus. **Military personnel are at especially high risk for tinnitus because they face very high-intensity impulse acoustic trauma such as explosions and weapons discharge, plus chronic exposure to loud noise.** Over the past decade, there has been growing evidence that hyperactivity of the central auditory system, particularly the auditory cortex, plays an important role in the genesis and maintenance of tinnitus. Repetitive transcranial magnetic stimulation (rTMS), which induces an electric field that inhibits hyperactive neurons, has emerged as a potential treatment. **This research project aims to evaluate and identify the primary source in the brain of unilateral (one-sided) tinnitus and determine the effectiveness of rTMS as a means for suppressing it.**

New Approaches to Overcoming Stress-Induced Delays in Wound Healing

Peter M. Elias, MD

Staff Physician, Dermatology Service, SFVAMC

Professor of Dermatology, UCSF

Highly increased psychological stress is a defining feature of military service, particularly under combat conditions. Psychological stress is also known to delay wound healing. This research study will use animal models to investigate the role of increased production of glucocorticoids—steroid hormones—in delaying wound healing. The study will also test which interventions that modify glucocorticoid-mediated mechanisms are most effective in normalizing delayed wound healing. Finally, the study will investigate the effectiveness of other therapeutic agents that have accelerated wound healing and counteracted the effects of glucocorticoids in preliminary studies. **Together, these investigations will determine the role of increased glucocorticoid levels in delaying wound healing, and assess a variety of potential treatments that could benefit wounded military personnel and the general public.**

Predicting Injury in US Army Warfighters

C. Seth Landefeld, MD

Staff Physician, Associate Chief of Staff
of Geriatrics and Extended Care, SFVAMC

Professor of Medicine, Epidemiology, and Biostatistics, UCSF

The overall goal of this research project is to identify predictors of injury in US Army warfighters serving in the Middle East combat theater, including Iraq and Afghanistan. The project has two specific aims: (1) To identify personal characteristics of US Army warfighters that are associated with serious injury or death while serving in the combat theater; and (2) to determine whether these characteristics serve as accurate predictors of injury after adjusting for the effects of warfighters' roles and duties in the combat theater. Several domains of independent variables will be evaluated as possible predictors of injury, including demographics such as age, gender, race, and education level; medical characteristics such as hypertension; psychosocial characteristics such as smoking or alcohol use; and extent of recent combat training before entering combat.

This research will provide a basis for classifying soldiers according to their risk of injury before they enter combat. Soldiers at higher risk may be candidates for preventive training or equipment. Also, this research may reveal non-combat related causes of combat injury, leading to novel approaches for preventing injury.

Possible Effects of Pesticide Exposure in the Persian Gulf Theater of War

S. Scott Panter, PhD

Research Chemist/Physiologist, Neurology Service, SFVAMC

Adjunct Assistant Professor of Neurological Surgery, UCSF

The men and women who served in the Gulf War were exposed to a broad range of chemical and biological agents that may have affected their health after the end of the war. In particular, widespread misuse of aerosolized pesticides may have led to the development of neurological disorders among these veterans because neurotoxic compounds that enter the nasal cavity can easily bypass the blood-brain barrier and cause tissue damage in the brain. **Military personnel currently deployed to the Persian Gulf are at risk of similar exposure.** This research study will evaluate the physical and behavioral effects of intranasally administered DEET and permethrin on animal models. This study is particularly important to currently deployed troops because if toxicity is noted after intranasal administration, the specific pesticides used in the Gulf, as well as patterns of pesticide usage, will have to be evaluated immediately.

Potential New Treatment for Arterial and Muscle Injury on the Battlefield

Rajabrata Sarkar, MD, PhD

Staff Physician, Surgical Service, SFVAMC

Assistant Professor of Surgery, UCSF

Tissue ischemia (inadequate blood supply), particularly severe ischemia of skeletal muscle, plays a significant role in both immediate and long-term limb loss following arterial and extremity injuries on the battlefield. **Significant advances in battlefield care have lowered the mortality of major vascular injuries, but subsequent limb dysfunction and loss from persistent muscle ischemia remain a problem.** This research project is intended to determine the potential clinical use of the enzymes MMP-2, MMP-9, and MMP-14, which are essential for regeneration of blood vessels and skeletal muscle, as immediate therapy following arterial injury or other muscle injuries. **This study will rigorously test the regenerative effects of these enzymes in clinically relevant models of arterial injury and skeletal muscle ischemia.**

Potential New Methods for Detecting Parkinson's Disease

Norbert Schuff, PhD

Senior Scientist, Radiology Service, SFVAMC

Associate Professor of Radiology, UCSF

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Although its exact cause is unknown, there is increasing evidence that exposure to environmental toxins and head trauma—for which military personnel are at increased risk—can play a major role in its later development. As new drugs to treat Parkinson's become available, it will become increasingly important to recognize and diagnose the disease as early as possible. The goal of this research project is to accurately diagnose Parkinson's disease with the use of two novel magnetic resonance imaging methods: susceptibility weighted imaging, which can directly measure brain iron, a key player in the etiology of Parkinson's, and diffusion tensor imaging, which can detect extremely subtle changes in brain tissue such as the disintegration of white matter fibers. Since the sensitivity of both these techniques increases considerably at higher field strength, these investigations will be carried out using the 4 Tesla MRI unit at SFVAMC. **It is expected that this study will help to identify new imaging markers for Parkinson's disease, which will improve diagnosis and potentially increase therapeutic options for the patient.**